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| DAIDS Bethesda, MD USA | POLICY | No.: DWD-POL-SR-01.00 |
| | Study Progress and Safety Monitoring | Page 1 of 10 |
| | Approval Date: 14 JUL 06 Effective Date: 01 NOV 06 | Replaces: None |

1.0 PURPOSE

This policy provides requirements for study progress and safety monitoring of all Division of AIDS (DAIDS) funded or sponsored clinical trials.

2.0 SCOPE

This policy applies to all DAIDS funded and/or sponsored clinical trials. It does not supersede existing DAIDS clinical research network policies and procedures for study progress and safety monitoring.

3.0 BACKGROUND

■ Relevant Policies

Study Progress and safety monitoring for all DAIDS-funded or sponsored clinical trials must be adherent with the following policies and guidelines:

- The NIH Policy for Data and Safety Monitoring issued on June 10, 1998 and Further Guidance on Data and Safety Monitoring for Phase I and Phase II Trials issued on June 5, 2000
- The current NIAID Clinical Terms of Awards, and any additional study-specific terms of award required by DAIDS
- Relevant ICH GCP guidelines (ICH-E6)
- Code of Federal Regulations (CFR), Title 45, Part 46: Protection of Human Subjects
- For trials with an US FDA IND, FDA IND regulations (CFR Title 21, Part 312)
- Any other regulations applicable to the specific trial, including for international trials, all requirements imposed by in-country regulatory and other appropriate authorities for study progress and safety monitoring

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4.0 DEFINITIONS

Division of AIDS (DAIDS) sponsored – DAIDS is responsible for the management and oversight of the trial, including submission of an Investigational New Drug Application (IND) to FDA, as applicable.

Division of AIDS (DAIDS) funded – DAIDS is providing financial support for trial or study.

Investigator of Record (IoR) – The person responsible for the conduct of the clinical trial at a clinical research site. This person is the signatory for the Form FDA 1572 (IND studies) or the DAIDS IoR Agreement (Non-IND studies). Written delegation of authority for specific trial responsibilities may be given to qualified individuals.

Principal Investigator (PI) – The qualified person designated by the applicant institution to direct the research for a trial. PIs oversee the scientific and technical aspects of a grant and the day-to-day management of the research.

For additional definitions, see the DAIDS glossary.

5.0 RESPONSIBILITIES

The Study PI is responsible to ensure that all DAIDS requirements for study progress and safety monitoring are met, and that appropriate documentation is kept and available for DAIDS site monitors and program staff review.

The DAIDS Program Officer (PO) working closely with the DAIDS Medical Officer/Medical Monitor for a trial is responsible for ensuring and documenting that all DAIDS requirements for study progress and safety monitoring have been met.

The DAIDS Medical Officer/Medical Monitor (MO/MM) is responsible for review of the protocol for all progress monitoring and safety aspects, approval of the Study Data Monitoring Plan (SDMP), and participation in study progress and safety monitoring to the extent specified in the Terms of Award for the grant, the study protocol, and the SDMP.

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6.0 POLICY

■ Study Data Monitoring Plan

All clinical trials funded or sponsored by DAIDS must have a Study Data Monitoring Plan (SDMP) approved in writing by the assigned DAIDS MO/MM before trial initiation. This plan is usually in addition to the relevant sections of the protocol document and is much more detailed. All DAIDS-sponsored or funded trials must have a study progress and safety review at least once a year for as long as participants continue on trial.

- The Study Data Monitoring Plan specifies:
 - The designated reviewer(s)/review committee for each type of report
 - The schedule for submission to reviewer(s)/review committees for each type of report
 - The types of study monitoring reports (see Appendix 1) may include:
 - Periodic study progress and safety reports for review by the study team (with no study arm-specific data)
 - Interim monitoring reports for review by independent study monitoring committees (includes study arm-specific data as applicable)
 - Periodic study progress and safety reports for review by designated individual study safety monitors (may include study arm-specific data as determined by the SDMP)
 - The contents of each report type, including the key parameters for assessment of study progress, feasibility, (including actual vs. expected accrual, participant losses, and event evaluability) quality, (including timeliness and quality of data submission) safety, futility, efficacy, and other outcomes, as appropriate

The characteristics of a SDMP are determined by the type of clinical trial to be monitored. The intensity of monitoring will primarily depend on the complexity, population, and risks involved with the trial. For example, Phase I trials must

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have very frequent and detailed monitoring of safety parameters in comparison to Phase III/IV trials. Well-defined rules for stopping accrual and study product administration may also be required for Phase I trials. A pre-specified plan for interim statistical analysis, including any necessary statistical adjustments for interim evaluations, is a required component of the overall study data monitoring plan.

Discussions regarding the SDMP should be initiated with the DAIDS MO/MM as soon as possible after award. Changes and additions requested by DAIDS must be adequately addressed by the study team. The DAIDS MO/MM assigned to the trial must give final approval to the SDMP before study initiation.

For a suggested SDMP template (most appropriate for Phase III/IV trials), see Appendix 2.

■ Types of Study Review Mechanisms

- The choice of the type of study review mechanism will be guided primarily by study phase and must be specified in the SDMP. DAIDS will determine which type of monitoring is appropriate for the trial based on the characteristics of the trial.
- The types of acceptable study progress and safety monitoring mechanisms are:
 - Data Safety Monitoring Board (DSMB)

A DSMB is an independent group of experts that advises DAIDS and the study investigators. The primary responsibilities of the DSMB are to periodically review and evaluate the accumulated study data for safety, quality of trial conduct, progress, feasibility, futility, and, when appropriate, efficacy. Based on these reviews, the DSMB makes recommendations to DAIDS concerning the continuation, modification, or termination of the trial.

All DAIDS-funded Phase III/IV trials require monitoring by a DAIDS-appointed DSMB. In rare instances, an alternative proposal for DSMB monitoring (with justification, charter, procedures, and membership) may be considered. For example, a new DSMB may be jointly instituted for a trial co-sponsored by DAIDS and another research agency. The proposed alternative must be approved in writing by the Director of the DAIDS Office for Policy in Clinical Research Operations or designee.

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All trials monitored by a DSMB must be reviewed by the Board at a minimum of once a year. All annual reviews will include reports addressing study progress and safety parameters. The DSMB must continue to review the trial for at least as long as any interventions continue to be compared. The study team or a Study Monitoring Committee (SMC, see below) may assume responsibilities for interim monitoring if follow-up continues after all trial comparisons have been terminated.

- DAIDS-appointed DSMBs

DAIDS appoints and supports several standing DSMBs to perform interim review of clinical trials. New trials will be assigned for monitoring to the most appropriate DSMB by DAIDS at the time of protocol review by a DAIDS scientific review committee. On a trial-specific basis, DAIDS may add *ad hoc* members as needed to a standing DSMB in order to address special aspects of the trial.

For a listing of the DAIDS standing DSMBs, see Appendix 3.

Standards for the membership and operations for each DSMB are specified by the DAIDS DSMB Charter, which also provides guiding principles for conducting reviews and making recommendations.

For the current charter for the DAIDS DSMBs, see Appendix 4.

- Study Monitoring Committee (SMC)

Typically, interim reviews for Phase II trials are performed by a DAIDS-approved SMC. However, DSMB review may be more appropriate for some randomized Phase II trials, e.g. trials that are large/multi-center, are blinded, are of particularly high risk or long duration, and/or involve vulnerable populations. Also, reviews by study teams may be acceptable for small Phase II trials in the early stage of study agent evaluation, but this must be specifically approved in writing by DAIDS before trial initiation.

An SMC is an independent group of experts that advises DAIDS and the study investigators for most Phase II trials. An SMC may also be the most appropriate monitoring mechanism for some Phase I trials. The primary responsibility of the SMC is to monitor participant safety. Roles and responsibilities are similar to those of a DSMB. However, SMCs

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have fewer members and perform more frequent interim reviews. An SMC must be able to convene on an *ad hoc* basis when immediate safety concerns arise. Investigators and DAIDS Program and Medical Officers may consider having at least one member of the SMC serve as an Independent Safety Monitor (ISM, see below). The DAIDS MO/MM may also be a non-voting member of the SMC. An SMC may also include one or two members of a standing DAIDS DSMB.

DAIDS may retain the primary responsibility for selection of the members and chairperson and for organizing the SMC, or DAIDS may delegate this responsibility to the study PI. If delegated to the PI, the proposed description, charter, operating procedures (including meeting/review schedule and venues), and roster (with CVs for each member and the chairperson) must be submitted at least 30 days before the projected date of study initiation and approved in writing by DAIDS before the trial may be initiated.

For DAIDS SMC Guidelines, see Appendix 5.

- Study Team Review, and in most cases, additional review by an Independent Safety Monitor (ISM)

For Phase I and other types of small-scale early evaluation trials of study agents, as well as some pharmacokinetic or proof-of concept studies, intensive monitoring by the study team is needed, but additional participation by an ISM is recommended. The ISM is a physician or other appropriate expert independent of the trial who is available to review SAEs, selected individual participant data, and cumulative safety data in a timely fashion. The ISM recommends appropriate actions regarding safe continuation of the trial to the study team and DAIDS. For trials outside of a DAIDS-funded network, a list of the designated safety reviewers from the study team must be submitted to DAIDS before trial initiation. Based on consideration of this list, addition of an ISM may be required by DAIDS.

For Phase II and III/IV trials, an ISM may also be an SMC or DSMB member. DSMBs and SMCs may consider designating one or more members as ISM(s) to review selected individual case SAEs on a continuous basis and/or cumulative safety reports between the scheduled full committee reviews. The ISM may work closely with the DAIDS MO/MM when performing these reviews.

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If the ISM is the sole independent reviewer for a trial (not a DSMB or SMC member) DAIDS may retain the responsibility to identify the ISM and define his/her role. Alternatively, DAIDS may delegate this responsibility to the study PI. If delegated, CV(s) for the persons(s) proposed to serve as the ISM(s) and a detailed description of his/her role as ISM must be submitted to DAIDS at least 30 days before the projected date of trial initiation. DAIDS must give written approval of the ISM and role before trial initiation.

For DAIDS ISM Guidelines, see Appendix 6.

- Other DAIDS Requirements for Independent Monitoring

- Submission of interim review reports to DAIDS

A written summary of the results of each independent interim monitoring review must be submitted to the DAIDS PO within 30 days after completion of the study progress and safety review. At minimum, these reports will be provided to DAIDS at the frequency of each review as specified in the SDMP.

For studies monitored by protocol teams without an ISM, the study PI is responsible for generating a brief summary monitoring report at least six-month intervals (or more frequently as specified in the SDMP) and whenever significant safety issues arise. The PI submits this report to the DAIDS PO for review and approval before any further distribution to site investigators, industrial collaborators, or regulatory agencies as appropriate.

- Support for SMC and ISM Activities

Necessary financial support for the activities of SMCs or ISMs must be obtained from the trial grant funding, unless another arrangement is reached with NIAID.

- International Trials and local Requirements

For international trials, all requirements for study progress and safety monitoring imposed by in-country regulatory and other appropriate authorities must be met by either the Study Team or Clinical Site Investigators, as appropriate. DAIDS may require submission of a plan for adherence with in-country regulations from the study PI or from the IoR for a clinical site as, applicable.

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- Relationship Between Safety Monitoring Mechanisms and Institutional Review Boards (IRBs) and Ethics Committees (ECs)
 - Once a safety monitoring mechanism is established for a trial, each of the relevant IRBs or ECs should be informed of the operating procedures with regard to study progress and safety monitoring (who, what, when, and how monitoring will take place). This information will serve to assure the IRB/EC that the safety of the research participants is appropriately monitored. If the IRB/EC is not satisfied with the monitoring procedures, it should request modifications. While it may not be possible to satisfy every IRB/EC completely, IRB/EC comments should be considered seriously.
 - Implementation procedures are provided in the NIH policy on "Guidance on Reporting Adverse Events to IRBs for NIH-supported Multicenter Clinical Trials" dated June 11, 1999 (<http://grants.nih.gov/grants/guide/notice-files/not99-107.html>). While this policy applies specifically to DSMBs, applicability should be considered for all study review mechanisms.
 - DAIDS will distribute a summary report for DSMB reviews to all participating investigators for submission to IRBs/ECs. Distribution of reports for SMC and appropriate ISM or study team reviews to site investigators will be the responsibility of the PI or designee, unless another arrangement is approved in writing by DAIDS.

7.0 REFERENCES

International Conference on Harmonisation, Guidance for Industry, E6 Good Clinical Practice: Consolidated Guideline
www.ich.org

Code of Federal Regulations, Title 21, Part 312 Investigational New Drug Application
http://www.access.gpo.gov/nara/cfr/waisidx_05/21cfr312_05.html

Code of Federal Regulations, Title 45, Part 46 Protection of Human Subjects
<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm>

NIH Policy for Data and Safety Monitoring issued on June 10, 1998
<http://grants.nih.gov/grants/guide/notice-files/not98-084.html>

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Further Guidance on Data and Safety Monitoring for Phase I and Phase II Trials issued on June 5, 2000

<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html>

NIAID Clinical Terms of Award

<http://www.niaid.nih.gov/ncn/pdf/clinterm.pdf>

NIH Guidance on Reporting Adverse Events to IRBs for NIH-supported Multicenter Clinical Trials issued on June 11, 1999

<http://grants.nih.gov/grants/guide/notice-files/not99-107.htm>

8.0 INQUIRIES

Questions and comments regarding this policy may be directed to the OPCRO Policy Group at:

NIAIDOPCROPOLICYGROUP@mail.nih.gov

9.0 AVAILABILITY

This policy is available electronically at the following URL:

<http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/Default.htm>

The signed original is maintained in the OPCRO policy office.

10.0 CHANGE SUMMARY

| Version # | Date | Replaces | Date of Revision | Rationale for Revision/Retirement |
|-----------|-----------|----------|---------------------|-----------------------------------|
| 1.0 | 14 JUL 06 | N/A | N/A | N/A |

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11.0 APPENDICES

Appendix 1 – Guidance on Study Monitoring Report

Appendix 2 – Study Data Monitoring Plan Templates

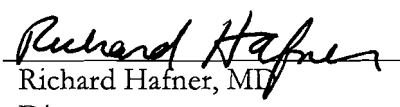
Appendix 3 – DAIDS Standing DSMB List

Appendix 4 – DAIDS Charter for DSMBs

Appendix 5 – DAIDS SMC Guidelines

Appendix 6 – DAIDS ISM Guidelines

12.0 APPROVAL

| | Signature | Program/Branch | Date |
|----------------|---|---|---------------|
| Authorized By: |  Richard Hafner, MD Director | Office for Policy in Clinical Research Operations | July 14, 2006 |